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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/230,195	12/10/1999	SUSANNA RYBAK	015280-28410	4712

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ELLEN L WEBER
TOWNSEND AND TOWNSEND AND CREW
TWO EMBARCADERO CENTER
8TH FLOOR
SAN FRANCISCO, CA 941113834

EXAMINER	
CHEN, SHIN LIN	
ART UNIT	PAPER NUMBER
1632	18

DATE MAILED: 01/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/230,195	Rybak et al.
Examiner	**Art Unit**
Shin-Lin Chen	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Nov 13, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 2, 4-35, 37, 38, and 40-42* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 2, 4-35, 37, 38, and 40-42* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11-13-02 has been entered.

It should be noted that the examiner for the present application has been changed, any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen.

Applicants' amendment filed 11-13-02 has been entered. Claim 3 has been canceled. Claims 1, 2, 14, 17, 20 and 26 have been amended. Claims 1, 2, 4-35, 37, 38 and 40-42 are pending and under consideration.

Claim Rejections - 35 USC § 101

1. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

2. Claims 37, 38 and 40 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility.

The specification fails to provide an asserted use that meets the requirement of 35 U.S.C. 101 for transducing a cell with a nucleic acid *in vitro* or inhibiting the growth of HIV in a cell by transducing said cell with a vector *in vitro*. There is no evidence of record for a specific utility or a well-established utility for transducing a cell with a nucleic acid encoding a viral inhibitor *in vitro* or inhibiting the growth of HIV in a cell by transducing said cell with a vector *in vitro*. The only readily apparent use for the claimed method is to study the effects of the method. The use of an invention as an object of further research or study does not meet the requirement of 35 U.S.C. 101.

Claims 37, 38 and 40 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

3. Claims 41 and 42 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims encompass cells contained within human beings, which are not considered patentable subject matter. See MEP. 2105. This rejection could be overcome by amending the claims to recite "An isolated cell" for example.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 2 and 42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "wherein the vector nucleic acid further encodes an HIV Rev binding subsequence" in claim 2 renders the claim indefinite. Claim 2 depends on claim 1 and claim 1 already comprises an HIV Rev binding subsequence. It is unclear whether the HIV Rev binding subsequence in claim 2 is the HIV Rev binding subsequence in claim 1 or there are two HIV Rev binding subsequences.

The phrase "selected from the group of cells comprising..." in claim 42 is vague and renders the claim indefinite. The term "comprising" is an open language that indicates there are other components in addition to the components recited in the claim. It is unclear what other components would be included in the group of claim 42. Changing the phrase "selected from the group of cells comprising..." to "selected from the group of cells consisting of..." would be remedial.

6. Claim 34 recites the limitation "the dicistronic mRNA" in line 4. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

> person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 1, 2, 4-35, 41 and 42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

Claims 1, 2, 4-24, 41 and 42 are directed to an HIV-based cell transduction vector comprising an HIV packaging site, a first viral inhibitor subsequence encoding ribonuclease, such as RNAse A and onconase, EDN, transdominant protein, or oncogene inhibitor etc., a splice donor (SD) site subsequence, a splice acceptor (SA) site subsequence, an HIV Rev binding subsequence and a promoter subsequence, wherein the first viral inhibitor subsequence is under the control of the promoter and is located between the splice donor and splice acceptor subsequences, and a cell comprising said vector. Claim 7 specifies the vector further comprises a cell binding ligand. Claims 9-13 specify the vector further comprises an IRES and/or a second viral inhibitor under the control of IRES. Claims 14-16 specify the vector comprises an HIV retroviral particle, or the vector nucleic acid is packaged in the HIV particle or in a liposome. Claims 25-35 are directed to a cell transduction vector comprising a nucleic acid subsequence encoding an EDN protein under the control of a promoter, wherein said cell transduction vector inhibits the replication of a retrovirus in a cell, such as CD4+ cells and stem cells, transduced by the cell transduction vector. Claims 30 and 31 specify the vector nucleic acid is packaged in a

retroviral particle and a liposome, respectively. Claims 32 specifies the vector comprises a cell binding ligand. Claims 33 and 34 specify the vector further comprises IRES and a multicistronic mRNA having two open reading frames under the control of a promoter, respectively.

The specification states "This invention relates to vectors for gene transfer and gene therapy, inhibition of viral and cancer cells by delivery of RNAs, recombinant cells and nucleic acids and the likes" (specification, p. 1 lines 11-13). The sole use of the claimed vectors as disclosed in the specification is for gene delivery and gene therapy. Thus, claims read on gene delivery or gene therapy *in vivo* in light of the specification. In addition, the phrase "the vector further comprises a pharmaceutical excipient" in claim 18 implies therapeutical use of the claimed vector. Claims 25-35 recite "wherein said cell transduction vector inhibits the replication of a retrovirus in a cell transduced by the cell transduction vector", therefore, the claims read on gene therapy *in vivo*.

The specification discloses inhibition of HIV replication by the combined expression of a Gag dominant negative mutant and EDN by transducing CEM cells with a tightly-controlled HIV-1 inducible vector *in vitro* and the anti-HIV activity of EDN in CEM cells as well as Jurkat cells *in vitro*. The claims encompass using the claimed HIV vector expressing various viral inhibitor, such as members of RNAse A superfamily, onconase, EDN, transdominant proteins, or oncogene inhibitors etc., for gene therapy via various administration routes *in vivo* so as to provide therapeutic effect for a particular viral disease in a subject. The specification fails to provide adequate guidance and evidence for how to use the claimed HIV vector for gene delivery

or gene therapy via various administration routes *in vivo* so as to provide therapeutic effect for a particular viral disease in a subject. The specification also fails to point out the correlation between the viral inhibitor encoded by the claimed vector and a particular viral disease such that the expression of said viral inhibitor *in vivo* could provide therapeutic effect for said particular viral disease.

The state of the art for gene therapy was unpredictable at the time of the invention. Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Verma states that "The Achilles heel of gene therapy is gene delivery, and this is the aspect that we will concentrate on here. Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression...The use of viruses (viral vectors) is powerful technique, because many of them have evolved a specific machinery to deliver DNA to cells, However, humans have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses." (e.g. p. 239, column 3).

Further, Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of

degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy (e.g. bridging pages 81-82). In addition, Gorecki, 2001 (Expert Opin. Emerging Drugs, 6(2): 187-198) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g. abstract). In view of the lack of adequate guidance and evidence and the unpredictability in gene transfer as discussed above, one skilled in the art at the time of the invention would not know how to use the claimed vectors expressing various viral inhibitors for gene delivery or gene therapy via any administration route*s in vivo* so as to provide therapeutic effect for a particular disease or disorder in a subject.

The specification also fails to provide adequate guidance for what SD or SA subsequence would have the same function as the consensus SD or SA sequence. The specification defines "subsequence" as a region of the nucleic acid equal to or smaller than the specified nucleic acid (specification, p. 12, lines 7-9). The consensus sequence for SA is (U/C).sub.nN(C/U)AG*G and the consensus sequence for SD is (C/A)AG*GU where * represents the splice site. It was known in the art that AG*G or AG*GU are essential part of SA and SD, respectively. The claimed SA or SD subsequence encompasses any sequence that is smaller than the consensus sequence of SA

or SD. However, the specification fails to provide adequate guidance and evidence that any SA or SD subsequence having nucleotide sequence lacking AG*G or AG*GU would still function as SA site or SD site for splicing. Thus, the specification fails to provide sufficient enabling disclosure for the full scope of the claimed SD or SA subsequence.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Applicants argue that claim 29 is drawn to a vector and the specification discloses how to make and use the vector in an *in vitro* environment (amendment, p. 6). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 112 first paragraph rejection.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.